HYPOPHOSPHATAEMIC OSTEOMALACIA IN THE ADULT WITH DEFECTIVE RENAL TUBULAR FUNCTION*

A REPORT OF FOUR CASES, WITH SPECIAL MENTION OF THE EFFECTS OF MASSIVE DOSES OF VITAMIN D (CALCIFEROL)

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Osteomalacia in the adult is usually the result of malabsorption of calcium by the intestinal tract. Sometimes, however, it is due to a defect in the convoluted tubules of the kidney: either a tubular acidosis or a defective reabsorption of phosphorus by the proximal cells of the tubules. This condition may form part of the syndrome first described by Fanconi (1936) in the child, and later by Girardet and Fanconi (1952) in the adult.

About thirty adult cases of Fanconi's syndrome have been recorded. Some of these appear to have been hereditary (Ben-Ishay, Dreyfuss, and Ullmann, 1961; Dent and Harris, 1956; Dent and Hodson, 1954; Stowers and Dent, 1947; Winters, Graham, Williams, McFalls, and Burnett, 1958). Others were secondary to multiple myeloma (Engle and Wallis, 1957; Muntendam, 1958; Sirota and Hamerman, 1954), nephrosis (Jonxis and Huisman, 1954; Stanbury and Macaulay, 1957), or heavy metal toxicity (Boudin, Barbizet, and Labram, 1959; Chisolm, Harrison, Eberlein, and Harrison, 1955; Clarkson and Kench, 1956; Morgan, Stewart, Lowe, Stowers, and Johnstone, 1962; Ravault, Roche, Lejeune, and Grandmottet, 1959; Wallis and Engle, 1957). The rest were of unknown aetiology.

In the four cases of resistance to vitamin D which are described below, the osteomalacia was not secondary to toxicity, nephrosis, or plasmocytosis; we had no opportunity of examining the urine of the patients' families, but the clinical data did not suggest that hereditary factors were involved. One of the four (Case 1) showed the generalized aminoaciduria typical of Fanconi's syndrome, and another (Case 4) had excessive urinary glycine.

The behaviour of our four cases is compared with that of a series of cases of osteomalacia complicating malabsorption syndromes. They were resistant to doses of vitamin D in the form of calciferol, and we had difficulty in finding the dose which was large enough to raise the serum phosphorus without promoting hypercalcaemia. Calciferol may be used to evaluate resistance to vitamin D in the following ways:

- (1) The tubule response can be established if a daily dose of calciferol does not raise the serum phosphorus.
- (2) The daily dose of calciferol which is necessary to correct hypophosphataemia can be used to measure the vitamin resistance of the kidneys.
- (3) If a rise in calciuria does not follow the administration of calciferol there must be a secondary resistance to the absorption of calcium by the intestinal tract.

Material

(1) **The Patients.**—Detailed case reports are given in the Appendix.

The four patients were all males and their ages ranged from 33 to 73 years. There was no evidence of dwarfism or of previous rickets.

(2) Clinical Data.

The symptoms were those usually observed in osteomalacia. Bone pains occurred in the pelvis, hips, thighs, ribs, and shoulders. The pain ceased on resting but was aggravated by movement or muscle tension, and it extended progressively, often symmetrically.

* Based on a paper read to the Heberden Society on November 30, 1962. (*Annals*, 1963, 22, 202.)

The gait became awkward and hesitant and resembled a duck's waddle; soon crutches were required and the patients then became bedridden. These defects seemed to be the result of muscle asthenia and there was a marked decrease in muscular strength without alteration of the reflexes or amyotrophias. This muscular weakness was so marked that one patient (Case 4) had been regarded as a case of myopathy, and another (Case 2) as a case of combined systemic disease of the pyramidal and posterior columns.

Sixty cases of malabsorption osteomalacia showed no similar muscle weakness.

Radiology.—Typical nodes like those described by Looser (1920) and Milkman (1934), often symmetrical were found in the usual sites: pelvis, hips, upper part of the thighs, ribs, and shoulder-blades. There were also deformities of the pelvic inlet, of the hips (coxa vara), of the thorax (bell form), and of the spine (kyphosis).

Histology.—Bone biopsy of the iliac crest showed hyperplasia of osteoid tissue.

Diagnosis.—The bone pains, disability, weakness, pseudo-fractures, and hyperplasia of osteoid tissue established the diagnosis of osteomalacia. The behaviour of the serum and urinary calcium and phosphorus pointed to a convoluted renal tubular defect as the chief cause of the condition.

Methods

Serum Calcium: Measured by the complexometric method (Schwarzenbach, 1952), with murexide as the indicator, and the spectro-photometric reading. The results are given in mg. per litre of serum.

Urinary Calcium: Measured by the same method, but with calcein as the indicator. The results, given as mg./24 hrs, represent the average of 3 to 6 days.

Serum Phosphorus: Measured by the technique of Fiske and Subbarow (1925).

Urinary Phosphorus: Measured by molybdic acid. Results represent the average of 3 to 6 days.

Calcium Infusion: Carried out by the method of Howard, Hopkins, and Connor (1953).

Calcium and Phosphorus Balance: Estimated by the technique of Reifenshtein and Albright (1948).

Serum Alkaline Phosphatase: Measured by the technique of Bodansky (1932), the results being given in Bodansky Units/100 ml. serum.

Results and Interpretation

(1) CALCIUM AND PHOSPHORUS METABOLISM

(a) Static Determination (Table I, opposite)

Serum Calcium: Normal or slightly decreased, only slightly different from the cases of malabsorption malacia.

Urinary Calcium: Normal in three cases and increased in one, whereas in cases of malabsorption osteomalacia the urinary calcium was always below 80 mg./day.

Serum Phosphorus: Very low, lower than the malabsorption cases.

Urinary Phosphorus: Normal.

Urinary/Serum Phosphorus Ratio: Greatly increased.

Phosphorus Clearance: Very high.

Phosphorus Reabsorption Rate (TRP): Down to 75 per cent. in two cases tested (Cases 1 and 2).

Serum Alkaline Phosphatase: Slightly raised in all four cases.

RESULTS OF INFUSION OF CALCIUM

Case No.	Calcium Infused (13 mg./kg.)	Calcium					
		Serum (mg./l.)		Urinary (mg./24 hrs)			Percentage of Calcium Infused
		Before	After 3 hrs	Before	Infusion Day	Increase	
1	880	93	120	287	537	+ 244	33
2	790	87	124	180	490	+ 310	39
3	880	98		246	457	+ 211	23
4	880	94	138	140	498	+ 358	40
Mean of 27 Cases of Malabsorption Osteomalacia	870	89 ± 6	122 ± 12	43 ± 22	154 ± 24	+ 111 ± 68	12 ± 9
Mean of 12 Normal Subjects	880 ± 220	98 ± 4	130 ± 11	136 ± 32	342 ± 55	+ 206 ± 71	24 ± 6

TABLE I

STATIC DETERMINATION OF CALCIUM, PHOSPHORUS, AND ALKALINE PHOSPHATASE

Case No	Age (yrs)	Sex	Date	Calcium		Phosphorus			Serum Alkaline Phosphatase (Bodansky units)	Clearance (ml./min)			Phosphorus Reabsorption (per cent.)
				Serum (mg./l.)	Urinary (mg./24 hrs)	Serum (mg./l.)	Urinary (mg./24 hrs)	Urinary/Serum Ratio		Urea	Creatinine	Phosphorus	
1	73	M	1961 1962 Mean	93 93 93	362 287 324	16 20 18	777 582 679	42 29 36	5.9 5.4 5.7	63	167	34	75
2	66	M	1960 1961 Mean	91 90 90.5	165 210 187	15 14 14.5	750 653 701	56 43 50	2.7 3.5 3.1	68	120	25.5	75.5
3	47	M	1958	96	215	15	823	53	4.5	80	140	35	
4	33	M	1957	98	137	16	621	33	5	72	137	34	
Mean of 42 Cases of Malabsorption Osteomalacia				87±6	46±21	24±4	530±165	20±7	9±5	55±14	108±27		

(b) Calcium Infusion Test (Table II)

Serum Calcium: The level was about the same both before and after the test as in normal subjects and cases of malabsorption osteomalacia.

Urinary Calcium: A marked increase followed the infusion; the calcium surplus represented 23 to 40 per cent. of calcium infused, whereas in cases of malabsorption osteomalacia it amounted only to 9 per cent.

Serum Phosphorus: After 3 hours the serum phosphorus increased (+7, +12, +5, and +6 mg./litre), but it did not reach the normal level, and after 6 hours fell to its original level. The process was the same in cases of malabsorption osteomalacia. In normal cases, the phosphataemia increase was greater after 6 hours.

Urinary Phosphorus: This decreased considerably in three out of four cases.

Urinary/Serum Phosphorus Ratio: This decreased in three of the four cases (−22, −20, −28), but did not fall to normal levels as in the cases of malabsorption osteomalacia.

(c) Calcium and Phosphorus Balances (Table III, overleaf)

(i) Calcium Balance

Case 1: The faecal calcium output was normal (77 and 74 per cent.), but the balance was negative because of the increased urinary calcium output (−208 and −105).

Case 2: The faecal calcium output was

II

SERUM AND URINARY CALCIUM AND PHOSPHORUS

					Phosphorus					
Serum (mg./l.)					Urinary (mg /24 hrs)			Urinary/Serum Ratio		
Before	After 3 hrs	After 6 hrs	Increase		Before	Infusion Day	Decrease	Before	Infusion Day	Decrease
			At 3 hrs	At 6 hrs						
17	24	23	+ 7	+ 6	826	446	− 380	48	26	− 22
14	24	22	+ 10	+ 18	630	385	− 245	52	32	− 20
15	20	20	+ 5	+ 5	950	700	− 250	63	35	− 28
20	26	21	+ 6	+ 1	622	572	− 50	31	22	− 9
23 ±4	29 ±4	27 ±5	+ 5	+ 4	487 ±143	396 ±163	− 91	20	16	− 4
37 ±6	46 +7	50 ±6	+ 9 ±3	+13 ±5	718 ±234	496 ±165	−225 ±228	19	13	− 6

TABLE III
CALCIUM AND PHOSPHORUS BALANCE IN THREE CASES

Case No.	Date	Calcium/24 hrs					Phosphorus/24 hrs				
		Intake	Faecal Output	Urinary Output	Balance	Faecal Output as Percentage of Intake	Intake	Faecal Output	Urinary Output	Balance	Faecal Output as Percentage of Intake
1	Mar. 1961 ..	678	524	362	-208	77	1,120	520	777	-77	42
	Feb. 1962 ..	712	530	287	-105	74	1,109	468	582	+59	42
2	Feb. 1961 ..	733	520	210	+3	71	1,110	431	653	+26	39
4	Dec. 1956 ..	806	912	140	-246	113	1,306	325	1,220	-237	24
	Jan 1957 ..	934	940	130	-136	100					

normal (71 per cent.), and the balance was even as the urinary calcium output was also normal.

Case 4: The faecal calcium output was higher than the intake, so that despite a normal urinary calcium output, the balance was negative (-246 and -136).

(ii) *Phosphorus Balance*

Cases 1 and 2: The faecal phosphorus output was normal (42 and 39 per cent.).

Case 4: The faecal phosphorus output was low, despite a very high faecal calcium output; the phosphorus balance was negative because of the high urinary phosphorus output.

(2) RENAL INVESTIGATIONS

The observations in these four cases (of a normal level of urinary calcium or a high level with normal calcaemia, of a very low serum-phosphorus level with normal urinary phosphorus (very high phosphorus clearance), and of the loss of 30 to 40 per cent. of the infused calcium) prompted the opinion that the osteomalacia was not due to intake deficiency or defective intestinal absorption of calcium.

Glycosuria.—Cases 1 and 2 showed a constant glycosuria, with a normal fasting blood sugar (0.8 to 0.9), and the glucose tolerance test gave normal responses in the blood. Glycosuria increased only in Case 1. Cases 3 and 4 showed no glycosuria, and the glucose tolerance tests were normal.

Amino Aciduria.—Qualitative evaluation was carried out by two-way chromatography (Dr. Frezal), and quantitative evaluation by measuring the urinary alpha-amino nitrogen (Table IV).

Case 1: Amino aciduria was greatly increased, with 1,260 mg. alpha-amino nitrogen per 24 hrs in the urine.

TABLE IV
AMINO ACID CHROMATOGRAPHY
(Two-way technique using phenol and collidine toluidine water.)

Acid	1	2	3	4
Alanine	++ ++	++		++
Arginine	+			
Aspartic	++ ++	+		+ +
Cystine	+	+		
Glutamic	+ ++	+		++
Glutamine	+ ++	+		+
Glycine	++ ++	++	+ +	++ ++
Histidine	++ +	+ +		
Hydroxyproline				
Leucine	+			
Lysine	+ +	+ +		+
Methylhistidine				
Methionine	+			
Phenyl alanine	+			
Proline				
Serine	++ ++	++	+	++
Taurine	+		++	
Threonine	+			
Tyrosine	++	+		+ +
Valine	+ +			
Urinary Alpha Amino Nitrogen (mg./24 hrs) ..	1,260	560	350	810

Case 4: Only the urinary glycine was much increased, with 810 mg. alpha-amino nitrogen per 24 hours in the urine; the other amino acids were normal.

Cases 2 and 3: No qualitative or quantitative abnormalities.

Other Renal Tubular Functions (Table V)

Cases 1, 2, 3: Serum CO₂ content slightly decreased.

Cases 2, 3, 4: Serum potassium slightly decreased.

TABLE V
TESTS OF RENAL FUNCTION IN FOUR CASES

Test	1	2	3	4
Proteinuria	0	0	0	0
Haematuria/min.	700	1,300	1,700	400
Blood Urea (g./litre)	0.25	0.30	0.35	0.30
Urea Clearance	63	68	80	72
Creatinine Clearance	167	120	140	137
Phenolsulphophthalein (percentage of intake lost in 70 min.)	59	68	67	72
Diuresis/24 hrs	1,600	1,700	1,300	1,200
Urinary Specific Gravity	1.014	1.020	1.018	1.024
Urinary pH	5.1	6.8	5.8	5.5
Titrateable Activity (mEq./litre)	40	25	24	41
Ammonia (mEq./litre)	50	32	56	45
Carbon dioxide Content (mEq./litre)	22	21	22	25
Serum Chloride (mEq./litre)	104	107	103	100
Serum Sodium (mEq./litre)	143	141	143	144
Serum Potassium (mEq./litre)	4.1	3.7	3.9	3.7

Renal Glomerular Functions.—There was no proteinuria, and the urea and creatinine clearances were normal.

(3) BONE BIOPSY

(a) 45 Specimens of Malabsorption Osteomalacia.—The thickness of the trabeculae was normal in 73 per cent. of the cases, and decreased only with age. The trabeculae were remodelled in 77 per cent., their edges were irregular in 55 per cent., and osteoclasts were noted in 16 per cent.

Beyond an abnormal amount of osteoid tissue, osteoblasts were active in 84 per cent.

Local fibrous metaplasia of the marrow was noted in 62 per cent.

(b) Four Cases under Consideration.—The cortical bone was thin and the Haversian canals enlarged. The trabeculae were thin and not remodelled, their edges were regular and lined by an abnormal amount of osteoid tissue, but the osteoblasts were flat. No fibrous metaplasia of the marrow was seen in these patients.

(4) EFFECTS OF CALCIFEROL ON PHOSPHORUS AND CALCIUM SAMPLES (Table VI)

(1) Effect of Standard Daily Doses of 3.5 mg.—Since 1956, we have used vitamin D₂ in the form of

TABLE VI
EFFECT OF VARIOUS DOSES OF CALCIFEROL ON PHOSPHORUS AND CALCIUM

Test	Case No.	Before Calciferol	After Calciferol (mg.)			
			30	60	90	120
Serum	1	21	24	24	23	
	2	14	19	17	19	
	3	16	18	18	19	18
	4	17	—	18	18	19
	Mean of 42 cases of malabsorption osteomalacia	26 ± 7	38 ± 8	43 ± 10	45 ± 7	45 ± 7
	1	682	792	779	710	
	2	701	698	660	666	
	3	760	868	900	855	820
	4	621	—	807	880	810
	Mean of 42 cases of malabsorption osteomalacia	20 ± 7	11 ± 4	11 ± 6	10 ± 4	9 ± 3
Phosphorus	1	29	30	29	28	
	2	50	37	39	35	
	3	47	48	50	45	45
	4	35	—	44	48	45
	Mean of 42 cases of malabsorption osteomalacia	20 ± 7	11 ± 4	11 ± 6	10 ± 4	9 ± 3
	1	93	98	96		
	2	91	88	92	92	
	3	95	98	98	98	98
	4	98	—	96	101	100
	Mean of 42 cases of malabsorption osteomalacia	42 ± 21	32 ± 23	32 ± 22	36 ± 26	36 ± 22
Calcium	1	287	230	272	264	
	2	165	430	408	422	
	3	209	228	259	260	252
	4	137	—	102	158	127
	Mean of 42 cases of malabsorption osteomalacia	42 ± 21	32 ± 23	32 ± 22	36 ± 26	36 ± 22

calciferol as a provocative test. We gave 15 mg. calciferol for 2 consecutive days; 6 and 7 days later we measured the serum and urinary calcium and phosphorus. If biological abnormalities persisted, we continued with this test, giving 3.5 mg. daily. We repeated the test each time the patient received a new dose of 30 mg. calciferol.

(i) *Effect of Calciferol on Phosphorus.*—In cases of malabsorption osteomalacia, very marked variations always occurred after a dose of 90 mg. calciferol. The serum phosphorus rapidly rose to over 38 mg. while the urinary phosphorus decreased. The ratio of urinary to serum phosphorus was lowered.

In our four cases, neither the serum nor the urinary phosphorus was modified by 30, 90, or even 120 mg. calciferol and the ratio of urinary to serum phosphorus stayed very high.

(ii) *Effect of Calciferol on Calcium.*—This dosage also failed to modify the serum calcium. Only in Case 2 did 30 mg. calciferol induce an important increase in urinary calcium (165 to 430 mg.).

(iii) *Effect of Calciferol on Faecal Calcium Clearance* (Table VII).—In Cases 1 and 4 there was

no change, but in Case 2 the percentage fell from 71 to 22 per cent.

In summary, the administration of calciferol did not very markedly modify the serum or urinary phosphorus of our four patients, who thus differed greatly in this respect from the cases of malabsorption osteomalacia. Nor was the faecal or urinary calcium modified, except that in Case 2 the urinary calcium output increased sharply, and in Case 4 the faecal calcium output decreased.

(2) *Effect of Very High Doses* (Table VIII).—In Cases 3 and 4 daily doses of 7.5 or 15 mg. calciferol did not modify the serum phosphorus or urinary calcium.

On a dosage of 30 mg./day the serum phosphorus began to rise slowly and reached normal after 3 weeks. The urinary calcium increased sharply in both cases, but the serum calcium was only very slightly affected.

The calcium balances were repeated several times, and Case 4 demonstrated that with 3.5 or 7.5 mg. calciferol the faecal calcium remained high, but with 30 mg. there was a marked decrease.

The hypercalcaemia enabled us to stop the calciferol therapy; and after an interval of 30 days the serum phosphorus fell to 19 mg. in Case 4, but remained at 28 mg. in Case 3.

TABLE VII
EFFECT OF ADMINISTRATION OF CALCIFEROL ON FAECAL CALCIUM RATE IN THREE CASES

Case	Before Calciferol			After Calciferol		
	Intake (mg./day)	Faecal Output		Intake (mg./day)	Faecal Output	
		(mg./day)	Percentage of Intake		(mg./day)	Percentage of Intake
1	712	530	74	686	489	71
2	753	540	71	824	187	22
4	806	912	113	1,088	1,066	98

TABLE VIII
EFFECT OF INCREASING THE DEGREE OF CALCIFEROL IN CASES 3 AND 4

Case No.		3				4			
Test		Calcium		Phosphorus		Calcium		Phosphorus	
		Serum	Urinary	Serum	Urinary/ Serum Ratio	Serum	Urinary	Serum	Urinary/ Serum Ratio
Before Calciferol		95	209	16	47	98	140	19	45
After Calciferol (mg./day)	7.5 during 10 days	98	252	18	45	102	152	20	42
	15 during 10 days	100	271	20	42	99	410	20	35
	30 during 12 days	101	650	27	38	100	456	27	38
	30 during 40 days	110	626	30	24	107	449	35	26
	0 during 30 days	101	83	28	61	102	197	19	64
	30 during 12 days	109	395	33	21	102	448	20	49
	30 during 30 days	—	—	—	—	110	617	36	37

Discussion

Clinically, the osteomalacia with defective renal tubular function is not very different from that due to malabsorption of vitamin D, but the two conditions are accompanied by very different biological characteristics of calcium and phosphorus metabolism, which assist differential diagnosis.

The serum phosphorus and urinary calcium levels and the effect of administering vitamin D in the form of calciferol are of particular importance.

CLINICAL CHARACTERISTICS.—The bone symptoms of the two conditions are very similar.

The neuro-muscular manifestations are significant. One of our four cases had long been regarded as myopathic, and another as suffering from a combined systemic disease of the pyramidal type. The other two showed muscular weakness, which has not been described in cases of malabsorption osteomalacia (Cooke, Barclay, Govan, and Nagley, 1947; Davies, Evans, Rees, and Fourman, 1958; Dent and Hodson, 1954; Lièvre and Bloch-Michel, 1955; Milne, Stanbury, and Thomson, 1952; Worthington and Mulder, 1959).

CALCIUM AND PHOSPHORUS METABOLISM

(1) Normal Calcaemia and Calciuria

(a) A normal serum calcium and, above all, a normal or high urinary calcium are not characteristic of malabsorption osteomalacia (the diagnosis of which is supported by low serum and urinary calcium levels), but rather suggest a defect of the convoluted renal tubules (Lichtwitz, de Sèze, Hioco, Bordier, and Parlier, 1960b; de Sèze, Lichtwitz, Ryckewaert, Bordier, Hioco, and Mazabraud, 1962). Moreover, our four patients were not able to retain the infused calcium, 30 to 40 per cent. of which was excreted in the urine, whereas the cases of malabsorption osteomalacia excreted only about 10 to 20 per cent. (Lichtwitz, de Sèze, Hioco, Bordier, and Mazabraud, 1960a).

(b) The low concentration of phosphorus in bone as well as in serum suggests that calcium cannot easily be fixed on the osteoid matrix. In support of this hypothesis, ingestion of a large amount of phosphorus reduces the calciuria to less than 80 mg. and a slight hypocalcaemia develops.

In Case 4, however, despite a normal calcaemia and calciuria, the calcium was not properly absorbed. Two others had a high level of urinary calcium and a normal faecal calcium output.

The calcium pool of a normal subject is provided

partly by intake and partly by osteolysis, which takes 1,000 to 1,200 mg. out of the bone; the daily accretion is equal to the osteolysis, so that the output is approximately equal to the intake.

In our four cases the osteolysis seemed to remain normal, but the accretion was decreased owing to the phosphorus concentration. The calcium drawn from the bone and not reattached maintains normal levels of calcaemia and calciuria, despite the decreased absorption. When there is no malabsorption, the exogenous calcium not attached to the bone joins the endogenous calcium and raises the urinary calcium output.

(2) Decreased Serum Phosphorus and Normal Urinary Phosphorus.

—These are not exclusively characteristic of renal tubular defect and are often detected in malabsorption osteomalacia. In both conditions, the phosphorus clearance is increased and the reabsorption rate decreased (Lichtwitz and others, 1960a), but these anomalies were more important in our four cases than in those of malabsorption osteomalacia; the phosphataemia was 20 mg. or less in only three out of fifty cases of the latter (Lichtwitz and others, 1960a).

(a) *Malabsorption Osteomalacia.*—The hyperparathyroid activity is regarded as the cause of the decreased phosphataemia (de Sèze and others, 1956a, b), for the following reasons:

(i) A parathyroid hyperplasia has often been found at autopsy (Erdheim, 1907; Liu, Ch'in, Chu, and Pai, 1940; Loewi, 1931; Luce, 1923; and Oberling and Guérin, 1931).

(ii) Histological observations of bone biopsies often show the characteristics of the parathyroid resorption, rehandlings, irregularities, Howships' lacunae, osteoclastic activity, and local fibrous metaplasia of the bone marrow (de Sèze and others, 1962). These characteristics may make it difficult to distinguish malabsorption osteomalacia from primary hyperparathyroidism.

(iii) There is an inverse relationship between calcaemia and phosphataemia, the lower the phosphataemia the higher the calcaemia. This is one of the most important aspects of hyperparathyroidism.

(iv) The decreased calciuria is only slightly less important than the calcaemia, because of an increased tubular reabsorption of calcium. Buchanan, Krintz, and Talmage (1959), Lichtwitz, de Sèze, Parlier, Hioco, and Bordier (1961), Talmage (1956), and even more recently McIntyre (1962), have shown this to be a result of parathyroid activity on the kidney.

(v) The influence of calciferol on the calcium and phosphorus samples can be easily explained as the effect of a sudden cessation of parathyroid activity. Another explanation could be the direct effect of calciferol on the tubular cells of the kidneys.

These five reasons have convinced us that the decreased serum phosphorus noted in malabsorption osteomalacia is due to hyperparathyroidism which is itself due to calcium deficiency.

(b) In the Four Cases Studied

(i) *Absence of Parathyroidism which could lead to Hypophosphataemia.*—The histological structure showed no signs of resorption: the trabeculae were often very thin and regularly lined like the cortical bone, there were no osteoclasts, and the marrow was fatty or normal.

Normal serum calcium with normal or even increased urinary calcium led us to think that there was no defect in the calcium reabsorption by the renal tubules.

(ii) *Renal Tubular Origin of Hypophosphataemia.*—Microdissections of the kidney of a child with Fanconi's syndrome showed important anatomical alterations of the proximal convoluted tubules which were short and stretched like a swan's neck (Clay, Darmady, and Hawkins, 1953).

Davies and others (1958), Stowers and Dent (1947), and Chisolm and others (1955) all found alterations in the proximal convoluted tubule cells.

Kidney biopsy is difficult to carry out as a routine test, so that the administration of calciferol can be used to diagnose kidney defects as the origin of the hypophosphataemia.

(2) Diagnosis and Measurement of Intestinal Vitamin Resistance.—Another form of vitamin resistance which may be associated with that of the kidney concerns absorption of calcium by the intestinal cells.

After only 30 mg. calciferol the urinary calcium of Case 2 suddenly rose to 400 mg., but that of the three others was unaffected (Table VI).

Calcium balance estimations showed, however, that in Case 2 the increased calciuria due to calciferol was balanced by an equal decrease in faecal calcium output (Table VII). In Cases 1 and 4 the faecal calcium output compared with the calcium intake stayed the same as before calciferol therapy, but the urinary calcium rose suddenly when the dose was raised to 30 mg./day, while the faecal calcium output showed a very marked decrease.

As the urinary output rises sharply, so the faecal output decreases, and one can say that, when the calcium absorption rises, the urinary calcium also rises.

As these modifications are produced in the same manner as in Cases 2 and 4, the only difference being the size of the necessary daily dose (the same size as the dose which reduces renal vitamin resistance), we think that 3.5 mg. calciferol will produce a hypercalciuria with a reduction in faecal calcium output, where there is no intestinal vitamin resistance. But if very large daily doses are necessary to bring about the same modifications, we believe that intestinal vitamin resistance is present.

Summary

VITAMIN D RESISTANCE

(1) Diagnosis and Measurement of Vitamin Resistance.—In a normal subject and in a case of malabsorption osteomalacia, calciferol increases the tubular reabsorption of phosphorus. In our four cases the calciferol did not modify the serum or urinary phosphorus levels, and the failure of the tubular reabsorption of phosphorus to respond to calciferol revealed the proper definition of the disease (Dent and Harris, 1956; Lichtwitz and others, 1960b; Salassa, Power, Ulrich, and Hayles, 1954; Stowers and Dent, 1947). But this so-called vitamin resistance is only relative if it can be overcome only by very high daily doses of calciferol.

For several years, we have observed that 90 mg. vitamin D₂ given in daily doses of 3.75 mg. was sufficient to raise the phosphataemia in all the malabsorption cases, but it did not modify any of the cases of hypophosphataemia consecutive to a kidney tubular defect.

The authors present their observations of four cases of hyperphosphataemic osteomalacia (Fanconi's syndrome) in the adult, in which they have studied the clinical, radiological, anatomical, biological, and renal characteristics and the calcium and phosphorus metabolism in comparison with some forty cases of osteomalacia due to the malabsorption of calcium.

The parathyroid or renal aetiology of the hypophosphataemia of these four cases is discussed in relation to bone biopsy, serum and urinary calcium, and phosphorus metabolic balance, and provocative tests with calciferol (vitamin D) administration.

They consider that the test with calciferol not only assists diagnosis, but also helps to evaluate the renal vitamin resistance with regard to the phosphorus and to discover intestinal vitamin resistance with regard to the calcium. The intestinal vitamin resistance is not always associated with renal vitamin resistance and seems to yield much earlier to strong doses of calciferol.

APPENDIX

Case Reports

Case 1, a man aged 71 years, complained first of bone pains in the knees. He soon required the aid of a crutch, and 6 months later, the pain extended to the hips and his gait became awkward and hesitant like a duck's waddle. At last, at age 73, the patient became bedridden. He also showed a marked muscular weakness without amyotrophie or neurological symptoms.

X rays showed the hips in coxa vara. The lower part of the thigh bone showed many small lacunae and the cortex was edged (Fig. 1). There were Looser fractures on the 10th and 11th ribs. Bone biopsies of the iliac crest and femoral shaft revealed large amounts of osteoid tissue.

Case 2, a man aged 63 years, had a sub-endocardial myocardial infarction. While he was in hospital pains started in the thighs. In the next 2 years a pyramidal syndrome developed, with normal cerebrospinal fluid and gastric achlorhydria. This strange neurological syndrome was diagnosed as combined systemic disease of the pyramidal and posterior columns.

One year later when aged 66, the patient returned to hospital, having been unable to walk for 6 months. He was also suffering from bilateral rib pains, and pains in the pubic bones and hips. *X* rays showed Looser fractures on the left thigh, the right pubis, the 6th, 7th, and 8th right ribs, and the 3rd, 4th, 5th, 6th, and 7th left ribs (Fig. 2, overleaf). An iliac crest biopsy revealed large amounts of osteoid tissue.

Case 3, a man aged 47 years, was sent to us by Dr. Leroy with a diagnosis of osteomalacia. He had already been suffering for 2 years from bilateral pains in the ribs and hips. After a year walking had become more and more difficult, and pains in the lower limbs were so acute that we suspected tabes, because at the age of 18 he had contracted a primary syphilis infection which had been treated for 15 years with bismuth.

There was also a muscular weakness of the iliopsoas and ischiotibialis groups. *X* rays showed Looser fractures in the 2nd, 3rd, 4th, 5th, 6th, and 7th ribs, and in the thighs. The vertebrae were flat, with the appearance of platyspondylitis (Fig. 3).

Fig. 3.—Case 3, flat vertebrae as in platyspondylitis.

Bone biopsy of the iliac crest revealed large amounts of osteoid tissue on all the edges of the trabeculae.

Fig. 1.—Case 1, lower femur and knee joint, showing small lacuna and many irregularities.

Fig. 2.—Case 2, bilateral symmetrical Looser fractures of ribs.

Case 4, a man aged 33 years, was first diagnosed as a case of spondylarthritis because he complained of sacro-iliac pains and stiffness of the spine. X rays showed enlargement and irregular edges of the sacro-iliac joints. The erythrocyte sedimentation rate was raised to 25 mm./1st hr. Phenylbutazone did not give relief. Myopathy was diagnosed because he could not sit up without the help of his arms and walked like a duck. There was a marked decrease of power in the iliopsoas, ischiotibialis and extensor pedis longus groups.

Despite various kinds of treatment, the pains, stiffness, and muscular weakness were unchanged. A new series of x rays then showed acute demineralization and many Looser fractures in the pelvis (Fig. 4, opposite), hips, thighs, ribs, and shoulders.

Biopsy showed that the trabeculae of the iliac crest were lined with large amounts of osteoid tissue (Dr. A. Mazabraud).

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Fig. 4.—Case 4, enlarged sacro-iliac joint with a Looser fracture starting at the joint and running up to the iliac crest.

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Ostéomalacie hypophosphatémique chez l'adulte avec fonction rénale tubulaire défectueuse
Rapport sur quatre cas avec mention spéciale des effets de l'administration de vitamine D (Calciférol)

RÉSUMÉ

Les auteurs présentent l'observation de quatre cas d'ostéomalacie hypophosphatémique (syndrome de Fanconi) chez l'adulte, chez lesquels ils ont étudié les caractéristiques cliniques, radiologiques, anatomiques, phospho-calciques, fonctionnelles rénales, et le métabolisme phospho-calcique, renseignements qu'ils ont comparé avec 40 cas d'ostéomalacie de type apport, par malabsorption intestinale du calcium.

L'origine parathyroïdienne ou rénale de l'hypophos-

phatémie est discutée à l'aide des renseignements fournis par les biopsies osseuses, les données du métabolisme phospho-calcique, et surtout par les réponses à l'administration de vitamin D₂ (Calciferol).

Les auteurs considèrent que le test au calciférol peut non seulement aider au diagnostic positif, mais également permettre d'évaluer la résistance rénale à la vitamine concernant la réabsorption du phosphore, permettent en outre de mettre en évidence une résistance intestinale à la vitamine concernant l'absorption du calcium. La résistance intestinale n'est pas toujours associée à la résistance rénale et semble céder plus rapidement aux fortes doses de calciférol.

Osteomalacia hipofosfatémica en el adulto con función renal tubular defectuosa
Informe sobre cuatro casos, con mención especial de los efectos de dosis masivas de vitamina D (Calciferol)

SUMARIO

Los autores presentan observaciones de cuatro casos de osteomalacia hipofosfatémica en adultos, en los cuales habían estudiado los rasgos clínicos, radiológicos, anatómicos biológicos y renales, así como el metabolismo del calcio y del fósforo en relación con osteomalacia debida a la absorpcion defectuosa de calcio.

Se discute la etiología paratiroidea a renal de la hipofosfatemia en los cuatro casos en relación con la biopsia ósea, el calcio sérico y urinario y el equilibrio metabólico del fósforo, así como el efecto de las reacciones de provocación mediante administración de calciferol (vitamina D).

Los autores consideran que las reacciones al calciferol no sólo contribuyen al diagnóstico sino tambien permiten la valoración de la restencia renal a la vitamina respecto al fósforo y el descubrimiento de la resistencia intestinal respecto al calcio. La resistencia intestinal a la vitamina no se ve siempre asociada a la resistencia renal a la vitamina y parece ceder mucho más pronto a fuertes dosis de calciferol.